UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/373,403	08/12/1999	WILLIAM R. ARATHOON	P1099C1	2534

23552 7590 05/23/2006

MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 05/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/373,403	ARATHOON ET AL.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-43, 45-51 and 53-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-43,45-51 and 53-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/21/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 3, 2006 has been entered.

2. The amendment filed March 3, 2006 is acknowledged.

Claims 30-43, 45- 51 and 53-55 are pending and examined on the merits.

The amendment to the specification is acknowledged. However, this amendment was previously requested in the preliminary amendment filed with the application on 8/12/1999.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims Rejections/Objections Withdrawn:

4. The objection to claim 52 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of the amendment canceling claim 52.

5. The rejection of claims 50 and 53-55 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record is withdrawn in view of the amendment.

Claim Rejections/Objections Maintained and New Grounds of Rejection:

6. The provisional rejection of claims 30-43, 45- 51 and 53-55 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 88-109 of copending Application No. 09/863,693 is maintained for the reasons of record. Applicants have indicated that upon an indication of allowable subject matter, a terminal disclaimer may be filed if appropriate.

7. The provisional rejection of claims 30-43, 45- 51 and 53-55 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 47-63 of copending Application No. 09/520,130 is maintained for the reasons of record. Applicants have indicated that upon an indication of allowable subject matter, a terminal disclaimer may be filed if appropriate.

8. The provisional rejection of claims 30-43, 45- 51 and 53-55 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 45-82 of copending Application No. 10/143,437 is maintained for the reasons of record. Applicants have indicated that upon an indication of allowable subject matter, a terminal disclaimer may be filed if appropriate.

9. The rejection of claim 51 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

Claim 51 has been amended to recite "each common light chains", which is grammatically incorrect. However, the indefiniteness comes because of the use of the word "each". In claim 50, from which claim 51 depends, there appears to be only one light chain, a "common light chain". The phrase "each common light chain[s]" implies that there is more than one common light chain. The specification defines the term "common light chain" on page 21 of the specification as referring "to the amino acid sequence of *the* light chain in the multispecific antibody of the invention". Therefore, the specification teaches that multispecific antibodies may only have one "common light chain".

10. Claims 30-42 remain rejected under 35 U.S.C. 112, first paragraph, on the grounds that the applicants were not in possession of the claimed inventions at the time of filing, because the disclosure of the specification fails to adequately describe the claimed genus of compounds to be made in the claimed methods and encoded by the nucleic acids of the claimed host cells is maintained for the reasons of record. This is a new matter rejection.

Applicants' arguments have been carefully considered but fail to persuade. Applicants point to page 97, line 28 – page 98, line 3 as support for the concept of multispecific antibodies comprising more than one light chain, where the light chains have at least 98% sequence identity and only differ from one another at amino acid positions outside of the CDR regions. The passage pointed to appears to be a discussion concerning whether one may substitute one light

chain for another in a specific scFv ("Alternatively, according to the invention, such light chains having 98-99% sequence identity with the light chain of a prospective paired scFv (Axl.78, for example) may be substituted with the paired light chain and retain binding specificity"). This sentence does not appear to be support for the concept of multispecific antibodies having more than one light chain, but instead appears to be support for making alternative versions of specific scFv molecules.

Applicants have also presented arguments that appear to be directed to enablement of the claimed inventions, when applicants assert that given the statement on pages 97-98, which concerns substitution of one light chain for another in an scFv, would enable one of skill in the art to use alternative versions of scFvs to make the claimed bispecific antibodies. However, the basis for this rejection is that the specification fails to provide written support for the claimed inventions because nowhere in the specification is there support for the concept of a bispecific antibody having two different light chains. Applicant is reminded that the description requirement is severable from the enablement requirement. Furthermore, it is noted that entitlement to a filing date does not extend to subject matter, which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Therefore, the rejection is maintained for the reasons of record.

The original rejection is reiterated below:

The basis for this rejection is that the amendment to the specification to recite claims drawn to methods of making multispecific antibodies comprising binding domains, where the

binding domains are made up of a heavy and light chain, and where the light chain is not the same for all of the binding domains is not supported by the specification. Therefore, the recitation of claim 30 "where the light chains of the first and additional polypeptides each have three CDR regions, and have at least 98% sequence identity and only differ from one another at amino acid positions outside of the CDR regions" is not supported by the specification as originally filed. The specification teaches methods of making multispecific antibodies, where the each of the binding domains comprises a "common light chain". The specification defines "common light chain" or "common amino acid sequence of the light chain" on page 21, and as an amino acid sequence of ***the*** light chain in the multispecific antibody. There does not appear to be any contemplation of multispecific antibodies comprising more than one light chain (i.e., there appears to be only the contemplation that the same light chain is used for all of the binding domains present in the multispecific antibody). Even a difference of 1 amino acid between the two light chains results in a bispecific antibody having two different light chains, and there is no support in the specification that demonstrates that applicant conceived of a method of making multispecific antibodies having two different light chains. Other instances in the specification that indicate that applicant conceived of methods of making bispecific antibodies where all of the binding domains comprise a light chain having the same sequence is found at page 10, lines 20-21; page 10, line 29 – page 11, line 1; page 12, line 15-line 24; page 13, lines 6-13; page 16, line 1-15; page 56, lines 13-29; page 95, lines 25-28; and page 103, lines 5-8.

Applicants have pointed to passages (page 97-98) in the specification and assert that these passages provide support for the concept of multispecific antibodies comprising light chains where the light chains have at least 98% sequence identity to each other and only differ

from one another at amino acid positions outside the CDR regions. However, this teaching of the specification appears to be directed to the process of selecting a light chain that will be used in the process of making a multispecific antibody (i.e. selecting a common light chain). The teachings on page 97 of the specification do not provide support for bispecific antibodies having two different light chains, but instead are directed to a process for identifying one light chain that may be useful in making a bispecific antibody. Applicants are reminded that the description requirement is severable from the enablement requirement.

11. Claim 39 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 39 depends from claim 30, which is drawn to methods for making multispecific antibodies. Claim 39 is drawn to a method for making an immunoadhesin ("wherein the antibody is a multispecific immunoadhesin"). However, the specification does not define multispecific antibodies to include species that are multispecific immunoadhesins. Immunoadhesins appear to be a separate type of molecule that is not encompassed by the term "antibody". Furthermore, in claim 30 the method requires that polypeptides be made that comprise binding domains, "the binding domain comprising a heavy chain and a light chain". Immunoadhesin molecules usually comprise fragments of heavy and light chains of antibodies (constant regions), and these constant region fragments do not comprise a binding domain (see Ashkenazi, A. et al, Proc. Natl. Acad. Sci. USA, 88: 10535-10539, 1991, page 10536, Fig. 1). Therefore, claim 39 appears to enlarge the scope of claim 30.

12. Claims 30-43, 45-49, 50, 51 and 53-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is indefinite because the phrase "the additional polypeptide" in part "(a)" lacks antecedent basis. This rejection would be overcome if this phrase were to be amended to "the at least one additional polypeptide".

Claim 30 is also indefinite because in part "(b)" first and additional polypeptides are described as comprising binding domains, which implies that the polypeptide forms an scFv. However, the phrase "comprising a heavy chain and a light chain" implies a construct comprised of two polypeptides. Therefore, the boundaries of claim 30 are unclear, because it appears that the claim, on the one hand, is drawn to a multispecific antibody made up of scFv constructs joined together by multimerization domains, but this is not clear because of the presence of the phrase "comprising a heavy chain and a light chain". If applicant intends for claim 30 to read on scFv constructs joined together by multimerization domains, then amending "comprising a heavy chain and a light chain" to "comprising a heavy chain variable domain and a light chain variable domain" would obviate this rejection. This rejection is also applied to claim 50 for the same reason.

Claim 37 is indefinite because of the phrase "wherein the first and additional polypeptide each comprise an antibody constant domain". This description will replace in claim 30 the phrase in "(a)" or in "(b)". It appears that applicant intends that this phrase replace the phrase in "(a)". Therefor, to obviate this rejection, applicants may amend claim 37 to recite "wherein the multimerization domain comprises an antibody constant domain".

Claim 43 is indefinite because of the first instance of "an interface". An interface of what? Claim 43 is also indefinite because of the first instance of "the interface". Because there are two interfaces, each interface needs a qualification. The rejections of claim 43 would be overcome if "(a)" were amended : "... a first polypeptide comprising a heavy chain variable domain from an antibody specific for a first antigen, and a multimerization domain forming an interface that comprises an altered amino acid residue in the interface, and selecting at least one additional nucleic acid encoding at least one additional polypeptide comprising a heavy chain variable domain from an antibody specific for a second antigen, and a multimerization domain forming an interface, wherein the interface of the at least one additional polypeptide has an amino acid residue that specifically interacts ...".

13. Claims 30, 40, 41, 43, 50 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Nissim (Nissim, A. et al., The EMBO Journal, 13(3): 692-698, 1994; cited in IDS) as evidenced by Merchant (Merchant, A.M. et al, Nature Biotechnology, 16: 677-681, 1998; cited in IDS).

Nissum teaches methods for expressing scFv fragments in *E. coli* from a phage library. Merchant teaches that the phage library of Nissum is library that has extensive H chain repertoires and unique L chain sequence, thus each antibody fragment derived from the phage library of Nissum has the same L chain. Nissum also teaches the making of "polyclonal" supernatants, which appear to be supernatants that contain scFv fragments with multiple specificities. In addition, Nissum teaches that multimerization occurs in the supernatants, especially when the supernatant has been concentrated (see 695, 2nd column). Nissum teaches

that for polyclonal scFv fragments, the supernatant was concentrated. The multimerization appears to occur through the binding of an L chain region from one chain binding to an H chain region from another chain. Therefore, Nissum teaches the claimed methods of producing multispecific antibodies. Nissum also teaches the isolated host cells of claim 41, because Nissum teaches how to make the E. coli that produce the scFv fragments (se page 697, 2nd column). Therefore, Nissum teaches that claimed inventions.

14. Applicants' request for an interview is acknowledged. However, due to time constraints, and interview could not be conducted before the mailing of this Office action. Applicants are invited to telephone the examiner to request an interview with the examiner and her supervisor before a response to this Office action is filed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
May 12, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER